## REMARKS

Claims 1-5, 7 and 9-23 are pending. No new matter has been added by way of the present submission. For instance, claims 1 and 20 have been amended to include subject matter taken from originally filed claims 6 and 8, now cancelled. The claims have also been amended to refer to a "charged" water-soluble drug and to remove reference to the symbol "~." Lastly, claim 3 has been amended to clarify that the charged water-soluble drug is retained in the nanoparticle when the composition is mixed with pancreatin as supported by claim 3 as originally filed. Thus, no new matter has been added.

In view of the following remarks, the Examiner is respectfully requested to withdraw all rejections and allow the currently pending claims.

### Request for Rejoinder

Applicants hereby request that claims 5 and 20-23 be rejoined. Claim 5 should be rejoined to the extent that it recites additional species belonging to the genus of "charged water-soluble drug" required in claim 1. Therefore, even though the Examiner has cited art relating to the elected species of "insulin" (which is not recited in claim 5), this rejection is improper and should never have been applied. Thus, examination should have occurred for all claimed species including the species of claim 5. Claims 20-23 should be rejoined to the extent that they recite a method for preparation of the allowable composition of claim 1.

### Issue with respect to Priority

The Examiner asserts that the claim of priority with respect to KR 10-2003-0096641 will not be honored since a certified copy thereof has not been provided. Applicants disagree and

submit that the present application is the U.S. National Phase of PCT/KR2004/003448, which properly claims priority to KR 10-2003-0096641. A certified copy of KR 10-2003-0096641 is therefore supplied by the International Bureau, thus satisfying this requirement. The Examiner is therefore requested to correctly recognize the claim of priority as being perfected. No translation thereof is required in order to perfect the claim of priority.

Objections to the Claims

The Examiner has objected to claims 1, 9-11 and 17-19 requesting clarification of the symbol "~." Applicants have addressed this issue in the above amendments, thus, this objection is moot. Reconsideration and withdrawal thereof are respectfully requested.

Issue under 35 U.S.C. § 112, second paragraph

The Examiner has rejected claim 3 under 35 U.S.C. § 112, second paragraph for the reasons recited at page 6 of the outstanding Office Action. Applicants respectfully traverse.

The Examiner has asserted that claim 3 is indefinite in regards to the limitation "wherein 80% or more of the water soluble drug is retained in the presence of pancreatin." Applicants have clarified this language to indicate that the charged water-soluble drug is retained in the nanoparticle when the composition is mixed with pancreatin, thus rendering this issue moot. Reconsideration and withdrawal thereof are respectfully requested.

Issues under 35 U.S.C. § 112, first paragraph

The Examiner has rejected claims 1-3, 6, 9-11, 15 and 17 under 35 U.S.C. § 112, first paragraph for the reasons recited at pages 7-11 of the outstanding Office Action. Applicants traverse.

The Examiner has asserted that the claims encompass any and all water soluble drugs without disclosing any structural or functional attributes of these drugs. The Examiner further rejects the claiming of "counter-ion substance," "lipids," "polymer" and "emulsifier." Applicants respectfully submit that those of skill in the art are fully able to recognize that Applicants were in possession of the full scope of claimed subject matter at the time of filing.

**Water-soluble drug, lipid, polymer and emulsifier**

The technical feature of the present invention is the reaction of the charged water-soluble drug with the counter-ion substance, and further with lipid, polymers, and emulsifiers. It does not necessarily rest on the specific kinds of water-soluble drug, lipid, polymer and emulsifier.

The present specification describes diverse examples of the water-soluble drug, lipid, polymer and emulsifier, and the Examples disclosed in more detail below provide enumerated preparations of an orally administrable nanoparticle composition containing insulin, counter-ion substance, lipid, polymer and emulsifier:

(i) the kind of water-soluble drug (particularly, page 11, lines 19 to 21 of the PCT/KR2004/003448);

(ii) the kind of lipid (page 13, lines 1-5), the use of lipid as a lipophilic carrier for entrapping water-soluble drug counter-ion substance complex (see, page 12, lines 12-16);

(iii) the kind of polymer (page 13, lines 7-15), the polymer as a substrate for forming matrix wherein the polymer surrounds surface of the lipid nanoparticle and is inserted between the lipid molecules and thus can prevent degradation of the lipid and a structural component of the nanoparticle (page 13, lines 19-22);

(iv) the kind of emulsifier (page 14, lines 8-19), and their use for stabilizing the dispersion (page 14, lines 17-19).

Thus, a skilled artisan can easily envision and understand that the present nanoparticle composition and the preparation thereof by using equivalents described in the present specification. Also, any charged water soluble drug can form an ionic complex with the specific counter-ion substance of claim 1, and a lipid and a polymer entrap the complex by hydrophobic interaction as described in the specification. Thus, a skilled artisan can select any lipid which can entrap the complex to the lipophilic carrier, any polymer which can inhibit the degradation of the lipid and components of the nanoparticle, and any emulsifier which can stabilize the particle so that they do not cluster with each other.

**The complex of a water-soluble drug and the method of ionically bonding**

The Examiner is of the opinion that the nature of association between the water-soluble drug and the counter-ion substance to form the complex is not apparent.

The present specification describes that the water-soluble drug may be ones charged in an aqueous solution, and the complex of the water-soluble drug and the counter-ion substance is obtained by reaction of the charged drug with the counter-ion substance (see page 11, line 21 to page 12, line 14 of WO 2005/061004). In other words, the complex can be formed by ionically bonding the ion in the charged water-soluble drug with the counter-ion in the substance. According to the amended claim 1, it becomes clear that the counter-ion substance is positively or negatively charged and the forming of a complex between counter-ion substances of a charged drug and a counter-ion substance thereof by ionic bonding.

Based on the above, any skilled artisan can clearly understand the nature of association between the water-soluble drug and the counter-ion substance.

In view of the above, Applicants respectfully request that the Examiner withdraw this rejection.

Issue under 35 U.S.C. § 102(b)

The Examiner has rejected claims 1, 2, 6, 7, 11-15 and 17-19 under 35 U.S.C. § 102(b) as being anticipated by EP 0771566 (hereinafter referred to as EP '566). Applicants respectfully traverse this rejection.

Applicants point out that claim 1 relates to an orally administrable composition containing nanoparticles with the particle size of 500 nm or less, comprising 0.1 to 30 weight% of a complex of a charged water-soluble drug and a counter-ion substance in which the charged water-soluble drug is ionically bonded with the counter-ion substance, wherein said counter-ion substance is an anionic compound selected from the group consisting of sodium salt of $C_{8-18}$ fatty

acid, sodium salt of bile acid, sodium alginate, and sodium carboxymethylcellulose, or a cationic compound selected from the group consisting of carnitine salt, benzalkonium chloride and cetrimide, 0.5 to 80 weight% of a lipid, 0.5 to 80 weight% of a polymer, and 1 to 80 weight% of an emulsifier, wherein the weight ratio of said lipid and said polymer is in the range of 1:0.05 to 3.

However, EP '566 fails to suggest or disclose such subject matter. Thus, there exists no anticipation. For instance, the following distinctions exist:

First, the present invention is applied to the charged water-soluble drug only, whereas EP '566 is applied to any kind of drugs such as charged and/or uncharged water-soluble and lipid-soluble drugs (see: the descriptions of EP '566, e.g. *The systems can be formulated in different ways to incorporate in their structure one or more active ingredients of a hydrophilic or lipophilic character.*).

Second, EP '566 does not teach or suggest the counter-ion substance as recited in the present claims. Such counter-ion substance reacts with the charged water-soluble drug to form a complex. Accordingly, a skilled artisan would have had no reason or motivation to consider EP '566 for preparing formulations for charged water-soluble drugs, wherein the drugs are not exposed to external chemical environment, e.g. pH or digestive enzymes, by entrapping them with lipids or polymers with high affinity with biological membranes.

Third, EP '566 relates to a process for the preparation of pharmaceutical compositions in the form of colloidal particles, and the colloidal particles are coated with a film made up of combination of cationic aminopolysaccharide and a phospholipid negatively charged. It relies on

the incorporation of lecithin, as a lipophilic surfactant, in the dispersed phase and of the chitosan, as a hydrophilic suspending, in the continuous aqueous phase. EP '566 provides colloidal particles with a positive charge by reacting lecithin and chitosan (see: page 2 of EP '566). In other words, the positively charged chitosan interacts with the negatively charged phospholipids to form a positively charged particle at the interface of the colloidal system. EP '566 also discloses that the inner structure of the systems is a) a reservoir system consisting of a oily surrounded or not by a polymer wall, and b) a matrix system consisting of solid particles containing none or little amounts of oil entrapped (see: page 3 of EP '566).

In contrast, in the present invention, the charged water-soluble drug (=active ingredients) reacts with the counter-ion substance to form a complex, and then the neutralized complex is entrapped by the hydrophobic bonding between the lipid and polymer. When the lipid/polymer nanoparticles are dispersed in an aqueous solution, the emulsifier may stabilize the dispersion.

In summary, EP '566 does not teach or suggest that the charged drug and complex thereof with counter-ion substance by ionic bonding. EP '566 describes the positively charged colloidal particles by reacting positively charged chitosan with negatively charged lecithin, and the positively charged particles are totally different from the neutralized complex of the present invention. Also, the forming pattern of inner structure is different from that of the present invention as mentioned above.

Thus, the presently claimed composition is not anticipated by the colloidal system of EP '566.

Issue under 35 U.S.C. § 103(a)

The Examiner has rejected claims 1, 2, 4 and 6-19 under 35 U.S.C. § 103(a) as being anticipated by WO 2004/043513 (hereinafter referred to as WO '513). Applicants respectfully traverse this rejection.

The purpose of WO '513 is to provide a controlled release system including a matrix composition for controlling the lag time and release rate of active ingredients. The matrix composition comprises a wax material, fat material, water sensitive material, and surface active material.

In contrast, the purpose of the present invention is to provide orally administrable nanoparticle compositions having an enhanced entrapping rate of water-soluble drugs within the nanoparticle composed of lipids and polymers, and the nanoparticle composition comprised a water-soluble drug, counter-ion substance, lipid, polymer and emulsifier.

Comparing the present invention with WO '513, the purposes and components of both inventions are different from each other. More specifically, the wax material working as a controlling material of the erosion rate, mechanical properties, and physical integrity of the matrix is an essential component of WO '513 whereas the nanoparticle composition of the present invention lacks the wax material. Thus, the essential components of the present invention are different from those of WO '513, and WO '513 does not mention or suggest any composition comprising the essential components of the present invention.

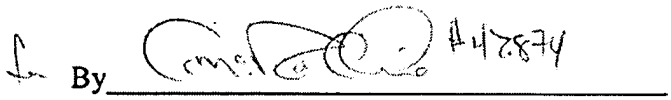
In view of the above, Applicants respectfully submit that the present claims define allowable subject matter. The Examiner is therefore respectfully requested to withdraw all rejections and allow the currently pending claims.

If the Examiner has any questions or comments, please contact Craig A. McRobbie, Reg. No. 42,874 at the office of Birch, Stewart, Kolasch & Birch, LLP.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to our Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under § 1.17; particularly, extension of time fees.

Dated: August 20, 2008

Respectfully submitted,

By  #42874

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